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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,149	11/17/2003	Robert H. Getzenberg	076333-0331	9439

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EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,149	GETZENBERG, ROBERT H.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *2-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/8/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Appendix 1*.

DETAILED ACTION

1. The response filed on 12/1/06 to the restriction requirement of 10/13/2006 has been received. Applicant has elected Group I, claim 1 as drawn to an antibody directed against RCCA-1 or immunogenic fragment thereof for examination without traverse.

2. Claims 1-16 are pending, notification of renumbering of the claims is in the restriction requirement of 10/13/2006.

3. In view of the teachings of the art Groups I-V of the restriction requirement of 10/13/2006 will be rejoined.

4. Claims 2-16 are hereby withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

5. Claim 1 is currently under consideration.

Priority

6. The priority data in the application data sheet should be updated to reflect the current status of the priority documents. See MPEP § 202.02.

Appropriate correction is required.

7. Examiner has established a priority date of 11/17/2003 for the instantly claimed serial number 10/713,149 because the claims as currently constituted recite molecular weights of about 53 kD, 32 kD, 27 kD, 20 kD, and 15 kD and a review of the parent applications does not reveal the claimed limitation. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Information Disclosure Statement

8. Applicant has stated that the documents listed in the information disclosure statement of 3/8/2004 have been previously submitted with application 09/850,128. Regretfully, a review of the contents of 09/850,128 and its parent case 09/050,991 revealed that the documents appear to have been submitted, but are no longer associated with the file. Thus, because they are not available to the examiner, lined out documents on the enclosed information disclosure statement have not been considered. Examiner would appreciate the resubmission of the references for review.

Specification

9. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Antibodies to the renal nuclear matrix proteins, RCCA-1-5.

10. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). The claimed subject matter that does not have antecedent basis in the specification are molecular weights of about 53 kD, 32 kD, 27 kD, 20 kD, and 15 kD. Because the claims as filed in the original specification are part of the disclosure, even though the material disclosed in the claims is not disclosed in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. In re Benno, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985). Thus amendment of the specification to include the material disclosed in the claims will obviate this objection.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 1, as written, does not sufficiently distinguish over an antibodies against RCCA-1-5 or an immunogenic fragment thereof as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). In order to obviate the instant rejection, the Examiner suggests that the claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" provided the support for such an amendment can be identified in the specification as originally filed. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. The term "about" in claim 1 is a relative term which renders the claim indefinite. The term "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Since the term "about" is not defined one cannot determine what the proteins bound by the claimed antibodies are or if the proteins are the same proteins or different proteins. For

example RCCA-5, with a molecular weight of about 15 kD and a pI of about 6.00, could be the same protein as RCCA-4, with a molecular weight of about 20 kD and a pI of about 5.25, given the indefinite nature of the claim. Similarly, RCCA-3, with a molecular weight of about 27 kD and a pI of about 6.5, could be the same protein as RCCA-2, with a molecular weight of about 32 kD and a pI of about 6.95, given the indefinite nature of the claim. Thus the metes and bounds of the claim cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

Claim 1 is drawn to an antibody directed against a nuclear matrix protein or an immunogenic fragment thereof in a human subject, wherein said protein is absent in normal renal cells but present in cancerous renal cells and is selected from the group consisting of: (a) RCCA-1 having a molecular weight of about 53 kD and a pI of about 9.30; (b) RCCA-2 having a molecular weight of about 32 kD and a pI of about 6.95; (c) RCCA-3 having a molecular weight of about 27 kD and a pI of about 6.50; (d) RCCA-4 having a molecular weight of about 20 kD and a pI of about 5.25; and (e) RCCA-5 having a molecular weight of about 15 kD and a pI of about 6.00 or an immunogenic fragment thereof.

The specification teaches that using 2-dimensional electrophoresis on nuclear matrix proteins from matched tumor and normal kidney tissue obtained from 17 renal cell cancer patients, five characteristic and unique nuclear matrix proteins were detected in all seventeen tumor samples which were absent in the samples of normal kidney tissue (RCCA 1-5) see p. 22, line 18 to p. 26, line 30 and Tables 1 and 2.

The specification teaches that a) RCCA-1 has a molecular weight of 53,000 kD and a pI of 9.30; (b) RCCA-2 has a molecular weight of 32,000 kD and a pI of 6.95; (c) RCCA-3 has a molecular weight of 27,000 kD and a pI of 6.50; (d) RCCA-4 has a molecular weight of 20,000 kD and a pI of 5.25; and (e) RCCA-5 has a molecular weight of 15,000 kD and a pI of 6.00, see Table 2.

One cannot extrapolate the teachings of the specification to the enablement of the claims because the molecular weight of a protein and isoelectric point does not uniquely identify a protein and is only an estimate of the protein molecular weight and isoelectric point and is subject to numerous variables that cannot be readily be predicted.

In particular, Kultima et al. (*BMC Bioinformatics* 2006, 7:475, www.biomedcentral.com/1471-2105/7/475) teach that in two-dimensional gel electrophoresis proteins first undergo isoelectric focusing (IEF) based on their net charge, then an orthogonal second dimension is applied to further separate proteins based on their molecular weight, in the presence of denaturing conditions. Furthermore, Kultima et al teach that two-dimensional gel electrophoresis mainly produces data which enables the investigator to determine whether a particular protein shows an increase or decrease when comparing two different conditions e.g. a diseased state compared to a non-diseased state. However, Kultima et al. teaches that the limited dynamic range and poor reproducibility between gels has been of major concern with traditional two-dimensional gel electrophoresis experiments, see 1st para. of Background Section. Furthermore Bondy et al. (Journal of Chromatography A, 2005, 1080:2-14) teach that although two-dimensional gel electrophoresis, the use of isoelectric focusing and sodium dodecyl sulfate-polyacrylamide gel electrophoresis, is a valuable tool for separating complex protein mixtures, its utility is often limited by lack of quantitative reproducibility, see p. 2, left column. Additionally, Bondy et al. teach that replicate runs of the same sample can have a standard deviation in spot position of the same order of magnitude as the distance between protein spots from complex mixtures, see p. 2, left column. Additionally, Sambrook et al. (Molecular Cloning, 2nd edition, Cold Spring Harbor Press, 1989, p. 18.47) teach that the determination of molecular weight by SDS-polyacrylamide gel electrophoresis (the second dimension in two-dimensional gel electrophoresis) is only an estimate and modifications of the polypeptide backbone, such as by glycosylation, can have a significant impact on the apparent molecular weight, see p. 18.47, 1st para.

Given the known art variability in the methods used to describe the proteins of claim 1, one of ordinary skill in the art would not predictably be able to identify the claimed proteins to which the antibody binds. The specification provides insufficient guidance with regard to these issues and no evidence has been provided which would allow one of skill in the art to make the invention as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to make and use the claimed invention without clear identification of the proteins to which the antibody would bind.

14. If Applicant was able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, Claim 1 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody directed against a **nuclear matrix protein** in a human subject, wherein said protein is absent in normal renal cells but present in cancerous renal cells and is and is selected from the group consisting of: (a) RCCA-1 having a molecular weight of about 53 kD and a pI of about 9.30; (b) RCCA-2 having a molecular weight of about 32 kD and a pI of about 6.95; (c) RCCA-3 having a molecular weight of about 27 kD and a pI of about 6.50; (d) RCCA-4 having a molecular weight of about 20 kD and a pI of about 5.25; and (e) RCCA-5 having a molecular weight of about 15 kD and a pI of about 6.00, does not reasonably provide enablement for an antibody directed against a nuclear matrix protein or **an immunogenic fragment** thereof in a human subject, wherein said protein is absent in normal renal cells but present in cancerous renal cells and is selected from the group consisting of: (a) RCCA-1 having a molecular weight of about 53 kD and a pI of about 9.30; (b) RCCA-2 having a molecular weight of about 32 kD and a pI of about 6.95; (c) RCCA-3 having a molecular weight of about 27 kD and a pI of about 6.50; (d) RCCA-4 having a molecular weight of about 20 kD

and a pI of about 5.25; and (e) RCCA-5 having a molecular weight of about 15 kD and a pI of about 6.00 or **an immunogenic fragment** thereof The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

Claim 1 is drawn to an antibody directed against a nuclear matrix protein or an immunogenic fragment thereof in a human subject, wherein said protein is absent in normal renal cells but present in cancerous renal cells and is selected from the group consisting of: (a) RCCA-1 having a molecular weight of about 53 kD and a pI of about 9.30; (b) RCCA-2 having a molecular weight of about 32 kD and a pI of about 6.95; (c) RCCA-3 having a molecular weight of about 27 kD and a pI of about 6.50; (d) RCCA-4 having a molecular weight of about 20 kD and a pI of about 5.25; and (e) RCCA-5 having a molecular weight of about 15 kD and a pI of about 6.00 or an immunogenic fragment thereof.

This means that one can predictably make and use antibodies to RCCA-1-5 or an immunogenic fragment thereof wherein said protein is absent in normal renal cells, but present in cancerous renal cells.

The specification teaches that using 2-dimensional electrophoresis on nuclear matrix proteins from matched tumor and normal kidney tissue obtained from 17 renal cell cancer patients, five characteristic and unique nuclear matrix proteins were detected in all seventeen tumor samples which were absent in the samples of normal kidney tissue (RCCA 1-5). The specification teaches that these nuclear matrix proteins were found in all the tumors irrespective of histological subtype or nuclear grade. The specification teaches that to rule out the possibility that the differences in nuclear matrix protein composition may be due to the detection of nuclear matrix proteins from stromal and other cell types admixed with the homogenized sample, the nuclear matrix protein composition of two renal cancer cell lines was also examined. The specification teaches that all five of the nuclear matrix proteins identified in the human tumor samples (RCCA 1-5) were also found in both the cell lines, see p. 22, line 18 to p. 26, line 30 and Tables 1 and 2.

One cannot extrapolate the teachings of the specification to the scope of the claims because one cannot predictably make antibodies that will bind to immunogenic fragments when the structure of the polypeptide comprised by the immunogenic fragments is unknown and undefined and given unpredictability of protein biochemistry and the well known unpredictability in the art of identifying immunogenic protein epitopes.

In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it

is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid alterations are possible in any given protein, the position within the protein's sequence where such amino acid alterations can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative alterations or no alterations. However, the specification provides no guidance on which of the broadly claimed immunogenic fragments comprise structure or residues that will be useful for the making of antibodies. The artisan is left to random experimentation in order to determine which of the broadly claimed immunogenic fragments will be useful for the making of antibodies to fragments of RCCA-1-5. Random experimentation is undue.

Furthermore, Flower (Trends in Immunology, 2003, 24: 667-674) teaches that the accurate prediction of immunogenic epitopes to which an antibody would bind is difficult and the complexity of immunogenic epitopes continually confounds efforts at prediction, see p. 667, right column. Additionally, Coleman et al. (Research in Immunology, 1994; 145(1): 33-36) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Further, Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444, see abstract in particular) teach single amino acid substitutions outside the antigenic site on a protein affects antibody binding.

Given the unpredictability of identifying protein epitopes and the sensitivity of antibody/antigen interactions to even single amino acid base changes and in the absence of any

information on the sequence of RCCA-1-5 or which fragments might be immunogenic, one of ordinary skill in the could not reasonably predict how to make antibodies to broadly claimed fragments of RCCA-1-5.

Although Applicant might argue that one of ordinary skill could screen for the RCCA-1-5 fragments that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir. 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

The specification provides neither information nor guidance on how to predictably make antibodies to immunogenic fragments of RCCA-1-5 when the structure of the broadly claimed immunogenic fragments is unknown and undefined. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

15. Claim 1 is rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claim 1 is drawn to an antibody directed against a nuclear matrix protein wherein said protein is absent in normal renal cells but present in cancerous renal cells and is selected from

the group consisting of: (a) RCCA-1 having a molecular weight of about 53 kD and a pI of about 9.30; (b) RCCA-2 having a molecular weight of about 32 kD and a pI of about 6.95; (c) RCCA-3 having a molecular weight of about 27 kD and a pI of about 6.50; (d) RCCA-4 having a molecular weight of about 20 kD and a pI of about 5.25; and (e) RCCA-5 having a molecular weight of about 15 kD and a pI of about 6.00 or an immunogenic fragment thereof. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of the RCCA-1-5 proteins defined by their molecular weight and isoelectric point, per Lilly by structurally describing a representative number of RCCA-1-5 proteins or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional

characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the RCCA-1-5 proteins defined by their molecular weight and isoelectric point in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any RCCA-1-5 protein defined by their molecular weight and isoelectric point, nor does the specification provide any partial structure of such RCCA-1-5 protein, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses the proteins RCCA-1-5, see Table 2, this does not provide a description of the proteins RCCA-1-5 defined by their molecular weight and isoelectric point that would satisfy the standard set out in Enzo.

The specification also fails to describe the proteins RCCA-1-5 defined by their molecular weight and isoelectric point by the test set out in Lilly. The specification describes only the proteins RCCA-1-5. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the proteins of RCCA-1-5 defined by their molecular weight and isoelectric point that is required to practice the claimed invention and thus the specification does not provide an adequate written description of antibodies to the claimed RCCA-1-5 proteins.

15. Claim 1 is rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claim 1 is drawn to an antibody directed against a nuclear matrix protein or an **immunogenic fragment** thereof in a human subject, wherein said protein is absent in normal renal cells but present in cancerous renal cells and is selected from the group consisting of: (a) RCCA-1 having a molecular weight of about 53 kD and a pI of about 9.30; (b) RCCA-2 having a molecular weight of about 32 kD and a pI of about 6.95; (c) RCCA-3 having a molecular weight of about 27 kD and a pI of about 6.50; (d) RCCA-4 having a molecular weight of about 20 kD and a pI of about 5.25; and (e) RCCA-5 having a molecular weight of about 15 kD and a pI of about 6.00 or an immunogenic fragment thereof. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of the immunogenic fragment of RCCA-1-5, per Lilly by structurally describing a representative number of immunogenic fragments of RCCA-1-5 or by describing "structural features common

to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the immunogenic fragment of RCCA-1-5 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any immunogenic fragment of RCCA-1-5, nor does the specification provide any partial structure of such immunogenic fragment of RCCA-1-5, nor any physical or chemical characteristics of the immunogenic fragment of RCCA-1-5, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses RCCA-1-5, see Table 2, this does not provide a description of immunogenic fragments of RCCA-1-5 that would satisfy the standard set out in Enzo.

The specification also fails to describe the immunogenic fragment of RCCA-1-5 by the test set out in Lilly. The specification describes only a RCCA-1-5. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the immunogenic fragment of RCCA-1-5 that is required to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Konety et al. (Journal of Urology, March 21, 1998, 159:1359-1363, IDS, see Appendix 1 for date), in view of Ausubel et al. (Short Protocols in Molecular Biology, 3rd ed. 1997, *Electroelution of Proteins from Stained Gels*, p. 10/33-10/35).

Claim 1 is drawn to an antibody directed against a nuclear matrix protein or an immunogenic fragment thereof in a human subject, wherein said protein is absent in normal

renal cells but present in cancerous renal cells and is selected from the group consisting of: (a) RCCA-1 having a molecular weight of about 53 kD and a pI of about 9.30; (b) RCCA-2 having a molecular weight of about 32 kD and a pI of about 6.95; (c) RCCA-3 having a molecular weight of about 27 kD and a pI of about 6.50; (d) RCCA-4 having a molecular weight of about 20 kD and a pI of about 5.25; and (e) RCCA-5 having a molecular weight of about 15 kD and a pI of about 6.00 or an immunogenic fragment thereof.

Konety et al. teach (a) RCCA-1 having a molecular weight of 53 kD and a pI of 9.30; (b) RCCA-2 having a molecular weight of 32 kD and a pI of 6.95; (c) RCCA-3 having a molecular weight of 27 kD and a pI of 6.50; (d) RCCA-4 having a molecular weight of 20 kD and a pI of 5.25; and (e) RCCA-5 having a molecular weight of 15 kD and a pI of 6.00 which are present only in human renal cell carcinoma tumor samples and were absent in all normal kidney tissue, see Table 2, p. 1361 left column, and Abstract.

Konety et al. does not teach antibodies to said proteins.

Ausubel et al. teach the isolation of proteins from polyacrylamide gels by electroeleution of the proteins from isolated gel fragments containing the protein, see p. 10/33-10/35.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one would have been motivated to isolate the proteins of Konety et al. using the conventional art method of Ausubel et al. to further characterize the proteins of Konety et al. because of their expression in renal cell carcinomas and not in normal kidney tissues, which indicates a role renal cell tumorigenesis, and the importance of understanding the functions of proteins involved in renal cell tumorigenesis to design better treatments for this disease.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art to have produced antibodies to the well known renal cell carcinoma protein antigens of Konety et al because the Board of Patent Appeals and interferences has taken the position that once an antigen has been isolated, the manufacture of antibodies against it is *prima facie* obvious. See Ex parte Ehrlich, 3 USPQ 2d 1011 (PTO Bd. Pat. APP. & Int. 1987), Ex parte Sugimoto, 14 USPQ 2d 1312 (PTO Bd. Pat. App. & Int. 1990).

Given that the prior art reference is co-authored by the inventor of the instant application, given that the proteins have the same MW and pI taught in the specification, given that the proteins are isolated from the same source as that taught in the prior art publication, one would have a reasonable expectation of success in producing antibodies that bind to the cited proteins.

Although the prior art reference does not specifically teach antibodies to the exemplified proteins, the antibodies of the combined prior art appear to be the same as the claimed antibodies. However, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the prior art and to establish patentable differences. See In re Best, 562 F2nd 1252, 195 USPQ 430 (CCPA 1977).

17. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of 11/17/2003 for the instantly claimed application

serial number 10/713,149, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

18. No is claim allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0890. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642
12/22/2006

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR

Appendix I

1: Konety BR et al. Identification of nuclear mat...[PMID: 9507884] Related Articles, Links

PMID- 9507884
OWN - NLM
STAT- MEDLINE
DA - 19980409
DCOM- 19980409
LR - 20041117
PUBM- Print
IS - 0022-5347 (Print)
VI - 159
IP - 4
DP - 1998 Apr
TI - Identification of nuclear matrix protein alterations associated with renal cell carcinoma.
PG - 1359-63
AB - PURPOSE: Neoplastic transformation, including renal cell carcinoma (RCC), is always accompanied by changes in nuclear morphology. Nuclear grading of RCC is based on characteristic alterations in nuclear shape, size, area and other morphologic parameters. The nuclear matrix, which forms the skeleton of the nucleus, determines nuclear morphology. Alterations in nuclear matrix protein (NMP) composition specific to tissue and cancer type have been described in a variety of human cancers. We conducted a study to analyze the nuclear matrix protein composition of renal cell carcinoma and compare it to that of normal renal tissue and renal cell carcinoma cells grown in culture. MATERIALS AND METHODS: We analyzed the nuclear matrix protein composition of RCC tumor tissue and that of normal kidney tissue obtained from seventeen patients undergoing radical nephrectomy for RCC. We also analyzed the NMP composition of two renal cancer cell lines (A-498 and 769-P). RESULTS: We were able to identify five different and unique NMPs which were present only in the human RCC tumor samples and were absent in all normal kidney tissue. One NMP was found specifically in the normal kidney tissue. All five RCC specific NMPs were also identified in the nuclear matrix of the two cell lines analyzed. CONCLUSIONS: Five nuclear matrix proteins specific and unique to RCC were identified. These NMPs are different from those previously identified in other tissues and neoplasms. The RCC specific NMPs identified in this study can potentially be used as diagnostic markers for renal cell carcinoma and for therapeutic tumor targeting.
AD - Department of Pathology, University of Pittsburgh Cancer Institute, University of Pittsburgh, Pennsylvania 15213, USA.
FAU - Konety, B R
AU - Konety BR
FAU - Nangia, A K
AU - Nangia AK
FAU - Nguyen, T S
AU - Nguyen TS
FAU - Veitmeier, B N
AU - Veitmeier BN
FAU - Dhir, R

Appendix I

AU - Dhir R
FAU - Acierno, J S
AU - Acierno JS
FAU - Becich, M J
AU - Becich MJ
FAU - Hrebinko, R L
AU - Hrebinko RL
FAU - Getzenberg, R H
AU - Getzenberg RH
LA - eng
GR - P30 CA47904/CA/NCI
PT - Journal Article
PL - UNITED STATES
TA - J Urol
JT - The Journal of urology.
JID - 0376374
RN - 0 (Antigens, Nuclear)
RN - 0 (Biological Markers)
RN - 0 (Nuclear Proteins)
SB - AIM
SB - IM
MH - Aged
MH - Antigens, Nuclear
MH - Biological Markers/analysis
MH - Carcinoma, Renal Cell/*chemistry
MH - Female
MH - Humans
MH - Kidney Neoplasms/*chemistry
MH - Male
MH - Middle Aged
MH - Nuclear Proteins/*analysis
MH - Research Support, Non-U.S. Gov't
MH - Research Support, U.S. Gov't, P.H.S.
EDAT- 1998/03/21
MHDA- 1998/03/21 00:01
AID - S0022-5347(01)63616-4 [pii]
PST - ppublish
SO - J Urol. 1998 Apr;159(4):1359-63.
